PHARMACEUTICAL COMPOSITION OF ANTIVIRAL AGENTS

RELATED APPLICATIONS

This application claims priority to European application No. EP 03029524.0, filed December 20, 2003; European Application No. EP 03016207.7, filed July 17, 2003; and European Application No. EP 03007071.8, filed March 27, 2003, each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition useful for the treatment of viral infections comprising a compound of the formula (I) and at least one antivirally active compound of the formula (II). Furthermore the present invention relates to a use of a compound of the formula (I) in combination or alternation with a compound of the formula (II) in the prophylaxis or treatment of a viral infection in a patient. The present invention also relates to a use of a compound of the formula (I) in combination with a compound of the formula (II) for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient. In addition the present invention relates to a kit of parts and to a manufacture for the prophylaxis or treatment of a viral infection in a patient.

BACKGROUND OF THE INVENTION

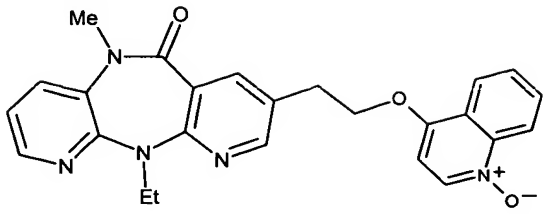
Human immunodeficiency virus (HIV) is recognized as the causative agent in AIDS.

Current therapies for HIV infection focus on inhibiting the activity of viral enzymes which are essential to the life cycle of the virus. The agents that are presently in use fall mainly into three classes, designated Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Protease

Inhibitors (PIs). Presently, combination therapies, i.e. the selection of two or more antiretroviral agents taken together to make up a "drug cocktail," are the preferred treatment for HIV infection. Combination therapies have been shown to reduce the incidence of opportunistic infections and to increase survival time. Typically, the drug cocktail combines drugs from different classes, so as to attack the virus at several stages in the replication process. This approach has been shown to reduce the likelihood of the development of virus forms that are resistant to a given drug or class of drugs.

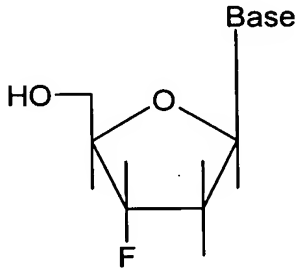
Treatment failure with rebound of the amount of HIV which can be measured in the blood is common for patients treated with combination antiretroviral regimens. Resistance to the drugs in the drug regimen develops as the virus replicates in the presence of these drugs. Because of structural similarities of the drugs within an antiretroviral class, cross resistance is commonly seen to the other members of that class (for example virologic failure on a regimen containing an NNRTI will lead to cross resistance to the other first generation NNRTI agents). As patients experience repeated virologic failure on antiretroviral combination therapy, their viruses develop broad multi-class antiretroviral drug resistance which limits the effectiveness of the next round of antiretroviral therapy. Many highly treatment experienced patients have been exposed to all three classes of antiretroviral drugs and cannot obtain two active drugs to form the core of a new, effective antiretroviral drug regimen.

A compound of the formula I:



wherein Me is methyl and Et is ethyl, or a pharmaceutically acceptable salt thereof, is described in the WO 01/96338 as showing activity against HIV-1 reverse transcriptase and thus being useful in the treatment of AIDS, ARC and related disorders associated with HIV-1 infection.

Furthermore compounds of the formula (II)

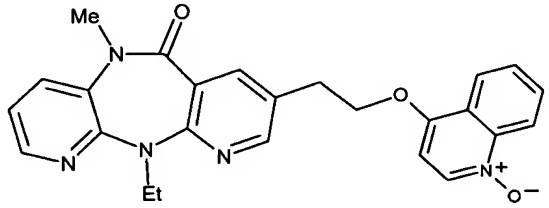


wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, are described in the WO 88/00050 and WO 91/01137 for the therapeutic and prophylactic control and treatment of AIDS, HIV infections, hepatitis B virus (HBV) infections and retrovirus infections in animals and man. These nucleoside compounds are transformed by cells or enzymes to triphosphates which inhibit the reverse transcriptase of retrovirus as well as the activity of DNA dependent polymerase of hepatitis B virus.

Combinations of a compound of the formula (I) with at least one compound of the formula (II) which exhibit potent therapeutic activity against HIV and HBV would greatly aid in the development of new combination therapy against human retroviral (HRV) infections and HBV.

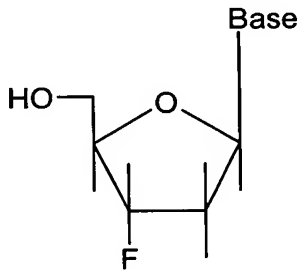
SUMMARY OF THE INVENTION

In one aspect, the present invention provides a novel pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising a compound of the formula (I)



wherein Me is methyl and Et is ethyl, or a pharmaceutically acceptable salt thereof;

and at least one antivirally active compound of the formula (II)



II

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

The pharmaceutical compositions of the present invention are useful in therapy, in particular as antivirals, especially

in the treatment or prophylaxis of human retroviral (HRV) infections.

In a second aspect, there is provided a use of a compound of the formula (I), as defined hereinbefore and hereinafter, in combination or alternation with at least one antiviral active compound of the formula (II), as defined hereinbefore and hereinafter, in the prophylaxis or treatment of a viral infection in a patient.

In a third aspect, there is provided a use of a compound of the formula (I), as defined hereinbefore and hereinafter, in combination with at least one antivirally active compound of the formula (II), as defined hereinbefore and hereinafter, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

In a fourth aspect of this invention, there is provided a kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprising:
(a) a first containment containing a pharmaceutical composition comprising a compound of the formula (I), as defined hereinbefore and hereinafter, and at least one pharmaceutically acceptable carrier, and
(b) a second containment containing a pharmaceutical composition comprising an antiviral active compound of the formula (II), as defined hereinbefore and hereinafter, and at least one pharmaceutically acceptable carrier.

In a fifth aspect of this invention, there is provided a manufacture comprising a compound of the formula (I), as defined hereinbefore and hereinafter, and at least one antiviral active compound of the formula (II), as defined hereinbefore and hereinafter, for use in combination or

alternation in the prophylaxis or treatment of a viral infection in patient.

With the combination of a compound of the formula (I) and a compound of the formula (II) according to this invention, including its use in prophylaxis and treatment, the person skilled in the art can achieve an advantageous therapeutic effect to inhibit viral replication, especially of human retrovirus (HRV) and HBV, in particular of multiresistant HIV. In most cases, the enhanced therapeutic effect is not attainable by administration of either agent alone. In a preferred but not necessary embodiment, the effect of administration of a compound of the formula (I) and a compound of the formula (II) in combination or alternation is synergistic. Even though a combination exhibits additive and not synergistic effects, the combination can still provide an effect that is different from the separate administration of the two agents. For example, the biodistribution, pharmacokinetics, cytotoxic effects or metabolism of one can be affected by the other.

Further aspects of the present invention become apparent to the one skilled in the art from the following detailed description and examples.

DEFINITIONS

The term "compound of the formula (I)" also comprises the pharmaceutically acceptable salts thereof.

The term "compound of the formula (II)" also comprises the pharmaceutically acceptable salts and prodrugs thereof.

The term "pharmaceutically acceptable salt" means a salt of the corresponding compound which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity,

irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, e.g., S.M. Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19, which is hereby incorporated by reference in its entirety.

As used herein, the term "treatment" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention to alleviate or eliminate symptoms of the viral infection and/or to reduce viral load in a patient.

As used herein, the term "prevention" or "prophylaxis" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood.

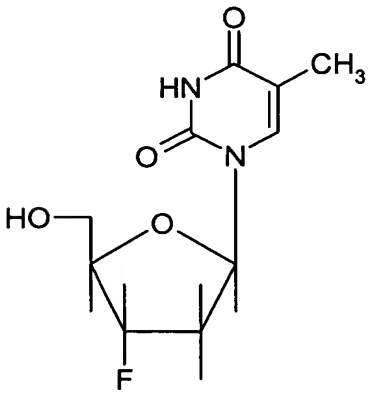
As used herein, the term "human retrovirus" (HRV) includes human immunodeficiency virus type I, human immunodeficiency virus type II, or strains thereof, as well as human T cell leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

DETAILED DESCRIPTION OF THE INVENTION

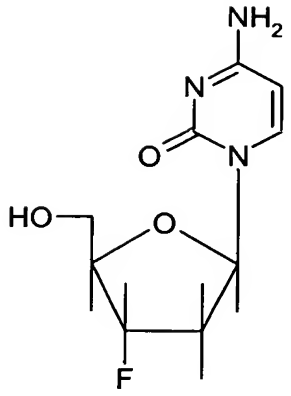
The virally active agents according to this invention may be in either free form or in protected form at one or more of the remaining (not previously protected) carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the art. Furthermore, the virally active agents according to this invention may also be used as in form of their pharmacologically acceptable salts and/or hydrates.

According to the first aspect of this invention, there is provided a novel pharmaceutical composition useful for the treatment of viral infections comprising a compound of the formula (I) and at least one compound of the formula (II).

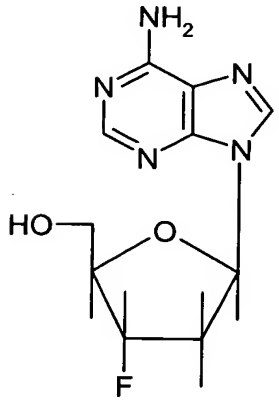
The following known compounds constitute part of the invention as preferred compounds of the formula (II) to be combined with a compound of the formula (I):



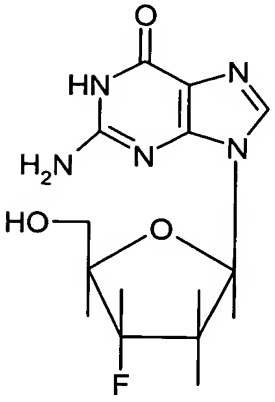
3'-deoxy-3'-fluorothymidine (FLT)



2',3'-dideoxy-3'-fluorocytidine



2',3'-dideoxy-3'fluoroadenosine



2',3'-dideoxy-3'-fluoroguanosine (FLG)

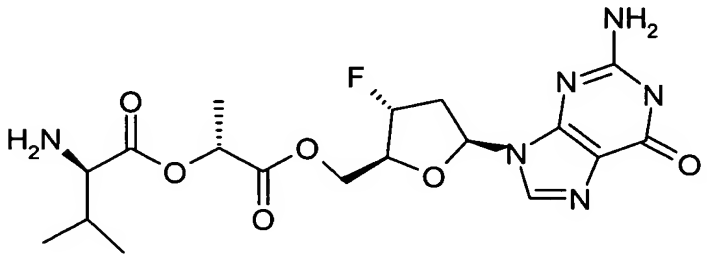
including pharmaceutically acceptable salts and prodrugs of the compounds listed above.

Preferred prodrugs of FLG are described in WO 99/09031 and WO 99/41268, which documents in their entirety are incorporated herein by reference.

The most preferred compound of the formula (II) to be combined with a compound of the formula (I) according to the aspects of this invention is selected from the group consisting of:
(a) 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and
(b) 2',3'-dideoxy-3'-fluoroguanosine (FLG), or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

The compound of the formula (II) is very most preferably selected from the group consisting of 3'-deoxy-3'-fluorothymidine and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, including pharmaceutically acceptable salts thereof.

3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine is a preferred prodrug of FLG and can be depicted by the following structure



The synthesis of 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, also named as 2',3'-dideoxy-3'-fluoro-

5-O-[2-(L-valyloxy)-propionyl]guanosine, is described in the WO 99/09031 and especially in example 32 therein.

Therefore, a preferred pharmaceutical composition useful for the treatment of viral infections comprises a compound of the formula (I) and 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

Furthermore, a compound of the formula (I) in combination or alternation with preferably 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, is used in the prophylaxis or treatment of a viral infection in a patient.

Also preferred is the use of a compound of the formula (I) in combination with 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

A preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises

(a) a first containment containing a pharmaceutical composition comprising a compound of the formula (I) and a pharmaceutically acceptable carrier, and

(b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A preferred manufacture comprises a compound of the formula (I) and a compound selected from 3'-deoxy-3'-fluorothymidine and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in a patient.

The advantageous effects of the combination of a compound of the formula (I) and the compound of the formula (II) are realized over a wide ratio, like for example in a ratio of between 1:250 to 250:1.

Therefore, in the compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention, a compound of the formula (I) and the at least one compound of the formula (II), which is preferably 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, are preferably present in a synergistic ratio. Usually, this ratio is between about 1:250 to about 250:1. More preferably the ratio is between about 1:50 to about 50:1. The most preferred ratio is between about 1:20 to about 20:1, which includes the ratios 1:18, 1:16, 1:14, 1:12, 1:10; 1:8; 1:6; 1:5; 1:4; 1:3; 1:2,5; 1:2; 1:1,5; 1:1,2; 1:1; 1,2:1; 1,5:1; 2:1; 2,5:1; 3:1; 4:1; 5:1; 6:1; 8:1; 10:1, 12:1, 14:1, 16:1, 18:1 and all ranges in between. If a further therapeutic agent is added, ratios will be adjusted accordingly.

It will be appreciated that the amount of pharmaceutical composition according to the invention required for use in treatment or prophylaxis will vary not only with the particular compound selected but also with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight

and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician or veterinarian. In general however the active compounds are included in the pharmaceutically acceptable carrier in an amount sufficient to deliver to a patient a therapeutically effective amount of compound to inhibit viral replication in vivo, especially HIV replication, without causing serious toxic effects in the treated patient. By "inhibitory amount" is meant an amount of active ingredient sufficient to exert an inhibitory effect as measured by, for example, an assay such as the ones described herein. A suitable dose will preferably be in the range of from about 0.05 to about 200 mg/kg of body weight per day.

The desired dose may conveniently be presented in a single dose or as divided dose administered at appropriate intervals, for example as two, three, four or more doses per day.

The pharmaceutical composition according to the present invention is conveniently administered in unit dosage form; for example containing 5 to 3000 mg, conveniently 5 to 1000 mg of active ingredient(s) per unit dosage form.

The pharmaceutical acceptable carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Examples of pharmaceutically acceptable carriers are magnesium stearate, chalk, starch, lactose, wax, gum or gelatin. Carriers which are suited to achieve a sustained release, for example natural or synthetic polymers or liposomes, are known to the one skilled in the art. Pharmaceutically acceptable carriers also comprise liquid

carriers and diluents, for example water, alcohol, glycerine or oil, which serve as a base for liquid formulations, such as solutions, suspensions or emulsions.

The compositions referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and therefore pharmaceutical formulations comprising a composition as defined above together with a pharmaceutically acceptable carrier comprise a further aspect of the invention.

The individual components of such compositions may be administered either in combination, i.e. simultaneously, or in alternation, i.e. sequentially, in separate or combined pharmaceutical formulations.

When a compound of the formula (I) is used in combination with a compound of the formula (II) against the same virus the dose of each compound may be either the same as or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compositions according to this invention preferably also comprise at least one pharmaceutically acceptable carrier.

According to the third aspect of this invention, the combination of a compound of the formula (I) and at least one compound of the formula (II) is used for the manufacture of a medicament for the prophylaxis or the treatment of a viral infection in a patient.

According to one embodiment, this medicament may be a unit dosage form, which is preferably useful in combination therapy, such as capsules or tablets. The unit dosage form contains a pharmaceutical composition according to this

invention, i.e. a compound of the formula (I) in combination with at least one compound of the formula (II), with at least one pharmaceutically acceptable carrier.

Therefore, another object of this invention also comprises bringing a compound of the formula (I) and at least a compound of the formula (II) together in conjunction or association with a pharmaceutically acceptable carrier.

According to another embodiment, this medicament is a multiple dosage form, preferably a kit of parts, which is especially useful in alternation and/or combination therapy to flexibly suit the individual therapeutic needs of the patient.

As a compound of the formula (I) is metabolized relatively rapidly by the cytochromes P450, especially the Cyp3A, it is preferred to co-administer an inhibitor of Cyp3A in order to obtain therapeutically effective blood levels of a compound of the formula (I). The use of ritonavir for this purpose is described in U.S. Patent 6,147,095. The use for this purpose of other inhibitors of Cyp3A is also possible. When administered in combination, a compound of the formula (I) and ritonavir can be formulated as separate compositions which are administered at the same time, or the compound of the formula (I) can be administered as a single composition.

Various doses of ritonavir have substantial and significant effects on a compound of the formula (I) by elevating, or enhancing, plasma concentrations of said compound. This pharmacokinetic drug interaction may offer the following advantages:

- enhanced antiviral activity of said compound,
- reduction of the administered dose of said compound,
- improved safety profile.

Therefore, according to one embodiment the combinations, compositions, kit of parts, manufactures of this invention and the uses thereof, which comprise said compound of the formula (I) and at least one compound of the formula (II), or a pharmaceutically salt or prodrug thereof, further comprise ritonavir. The compound of the formula (II) is preferably selected from the group consisting of (a) 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and (b) 2',3'-dideoxy-3'-fluoroguanosine (FLG), or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

Following this, a preferred pharmaceutical composition useful for the treatment of viral infections comprises a compound of the formula (I) in combination with ritonavir and a compound selected from the group consisting of 3'-deoxy-3'-fluorothymidine and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

Furthermore, a compound of the formula (I) in combination with ritonavir and in combination or alternation with preferably 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, is used in the prophylaxis or treatment of a viral infection in a patient.

Also preferred is the use of a compound of the formula (I) in combination with ritonavir and a compound selected from the group consisting of 3'-deoxy-3'-fluorothymidine and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, for the

manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

A preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises:
(a) a first containment containing a pharmaceutical composition comprising a compound of the formula (I) and ritonavir and a pharmaceutically acceptable carrier, and
(b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Another preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises:
(a) a first containment containing a pharmaceutical composition comprising a compound of the formula (I) and a pharmaceutically acceptable carrier, and
(b) a second containment containing a pharmaceutical composition comprising ritonavir and a pharmaceutically acceptable carrier, and
(c) a third containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A preferred manufacture comprises a compound of the formula (I), ritonavir and a compound selected from the group consisting of 3'-deoxy-3'-fluorothymidine and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in a patient.

In said combinations, compositions, kit of parts, manufactures, which comprise a compound of the formula (I), ritonavir and at least one compound of the formula (II), preferably 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically salt thereof, the ratio and the amount of a compound of the formula (I) and ritonavir present in these combinations are preferably chosen to achieve therapeutically effective plasma levels of said compound. Dosage regimens are described in the US 60/433690, including patent applications claiming the priority of US 60/433690, and may be optimized in view of the combination with the compounds of the formula (II) according to known methods.

According to further embodiments the combinations, compositions, kit of parts, manufactures of this invention and the uses thereof comprise a combination selected from the group consisting of:

- a compound of the formula (I), a compound of the formula (II) and one, two or more further NRTIs;
- a compound of the formula (I), a compound of the formula (II), a protease inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), a compound of the formula (II), an entry inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), a compound of the formula (II), a protease inhibitor, an entry inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), a compound of the formula (II), a protease inhibitor, an integrase inhibitor and optionally one, two or more further NRTIs.

In the above listed combinations, compositions, kit of parts, manufactures and uses thereof the compound of the formula (I) may advantageously be combined with ritonavir as described hereinbefore.

In the foregoing and in the following, the term "further NRTI" refers to a nucleoside reverse transcriptase inhibitor, or a pharmaceutically acceptable salt or prodrug thereof, other than the selected compound of the formula (II). Examples of further NRTIs are Abacavir Sulfate (Ziagen), Didanosine (ddI, Videx), Emtricitabine (Emtriva), Lamivudine (3TC, Epivir), Stavudine (d4t, Zerit), Tenofovir disoproxil fumarate (nucleotide, bis (POC) PMPA, Viread), Zalcitabine (ddc, Hivid), Zidovudine (AZT, Retrovir), Amdoxovir (DAPD; Gilead Sciences), Elvucitabine (ACH-126443; Achillion Pharm.), GS-7340 (Gilead Sciences), INK-20 (thioether phospholipid formulation of AZT; Kucera Pharm.), MIV-310 (Medivir AB), MIV-210 (Medivir AB), Racivir (racemic FTC; Pharmasset), Reverset (RVT, D-D4FC, DPC-817; Pharmasset), SPD-754 ((-)dOTC; Shire Pharm), BCH-13520 (Shire Pharm) and BCH-10618 (Shire Pharm).

In the foregoing and in the following, the term "protease inhibitor" refers to a protease inhibitor, or a pharmaceutically acceptable salt or prodrug thereof. Examples of protease inhibitors are Amprenavir (VX-478, Agenerase), Atazanavir (Reyataz), Indinavir Sulfate (MK-639, Crixivan), Lexiva (fosamprenavir calcium, GW -433908 or 908, VX-175), Lopinavir + Ritonavir (ABT-378/r, Kaletra), Nelfinavir Mesylate (Viracept), Ritonavir (ABT-538, Norvir), Saquinavir (Invirase, Fortovase), Tipranavir + Ritonavir, AG-1776 (JE-2147, KNI-764; Nippon Mining Holdings), AG-1859 (Pfizer), DPC-681/684 (BMS), GS224338 ('4338; Gilead Sciences), KNI-272 (Nippon Mining Holdings), Nar-DG-35 (Narhex), P(PL)-100 (P-1946; Procyon Biopharma), P-1946 (Procyon Biopharma), R-944 (Hoffmann-LaRoche), RO-0334649

(Hoffmann-LaRoche), TMC-114 (Johnson & Johnson), VX-385 (GW-640385; GSK/Vertex) and VX-478 (Vertex/GSK).

In the foregoing and in the following, the term "entry inhibitor" refers to an entry inhibitor, including fusion inhibitors, inhibitors of the CD4 receptor, inhibitors of the CCR5 co-receptor and inhibitors of the CXCR4 co-receptor, or a pharmaceutically acceptable salt or prodrug thereof. Examples of entry inhibitors are AMD-070 (AMD-11070; AnorMed), BlockAide/CR (ADVENTRX Pharm.), BMS 806 (BMS-378806; BMS), Enfurvirtide (T-20, R698, Fuzeon), KRH-1636 (Kureha Pharmaceuticals), ONO-4128 (GW-873140, AK-602, E-913; ONO Pharmaceuticals), Pro-140 (Progenics Pharm), PRO-542 (Progenics Pharm.), SCH-D (SCH-417690; Schering-Plough), T-1249 (R724; Roche/Trimeris), TAK-220 (Takeda Chem. Ind.), TNX-355 (Tanox) and UK-427,857 (Pfizer).

Examples of an integrase inhibitors are L-870810 (Merck & Co.), c-2507 (Merck & Co.) and S(RSC)-1838 (Shionogi/GSK).

According to still further embodiments the combinations, compositions, kit of parts, manufactures of this invention and the uses thereof comprise a combination selected from the group consisting of a compound of the formula (I), a compound of the formula (II) and a further antiviral agent. In these still further embodiments the compound of the formula (I) may advantageously be combined with ritonavir as described hereinbefore.

A further antiviral agent may be selected from the group of the maturation inhibitors, antisense compounds or NNRTIs, other than a compound of the formula (I). Examples of further antivirals are PA-457 (Panacos), KPC-2 (Kucera Pharm.), HGTV-43 (Enzo Biochem), Delavirdine (Rescriptor), Efavirenz (DMP-266, Sustiva), Nevirapine (BIRG-587, Viramune), (+)- Calanolide A and B (Advanced Life Sciences),

Capravirine (AG1549, S-1153; Pfizer), GW-695634 (GW-8248; GSK), MIV-150 (Medivir), MV026048 (R-1495; Medivir AB/Roche), NV-05 (Idenix Pharm.), R-278474 (Johnson & Johnson), RS-1588 (Idenix Pharm.), TMC-120/125 (Johnson & Johnson), TMC-125 (R-165335; Johnson & Johnson), UC-781 (Biosyn Inc.) and YM-215389 (Yamanoushi).

The combinations, compositions, kit of parts, manufactures of this invention and the uses thereof of the above mentioned embodiments may be combined with further active ingredients.

Examples of such further active ingredients are acyclic nucleosides such as acyclovir, ganciclovir; interferons such as alpha-, beta- and gamma-interferon; glucuronation inhibitors such as probenecid; nucleoside transport inhibitors such as dipyridamole; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, ampligen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as 2-deoxy-D-glucose, castanospermine, 1-deoxynojirimycin; and inhibitors of HIV binding to CD4 receptors such as soluble CD4, CD4 fragments, CD4-hybrid molecules and inhibitors of the HIV aspartyl protease such as L-735,524.

The further antiviral agent is preferably chosen from zidovudine, didanosine, zalcitabine, stavudine, lamivudine, lopinavir, delavirdine, including delavirdine mesylate, nevirapine, delavirdine, efavirenz, indinavir, nelfinavir, including nelfinavir mesylate, amprenavir and saquinavir, including saquinavir mesylate.

The compounds, or their pharmaceutically acceptable derivative or salts thereof, can also be mixed with other active materials that do not impair the desired action, or

with materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatorics, protease inhibitors, or other nucleoside or non-nucleoside antiviral agents, as discussed in more detail above.

In general, during alternation therapy, an effective dosage of each agent is administered serially, whereas in combination therapy, an effective dosage of two or more agents are administered together. The dosages will depend on such factors as absorption, biodistribution, metabolism and excretion rates for each drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Examples of suitable dosage ranges for a compound of the formula (I), compounds of formula (II), of ritonavir, of further NRTIs and other antivirals can be found in the scientific literature. Many examples of suitable dosage ranges for other compounds described herein are also found in the public literature or can be identified using known procedures. These dosage ranges can be modified as desired to achieve a desired result.

It has been recognized that drug-resistant variants of HIV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in the viral life cycle, and most typically in the case of HIV, in either the reverse transcriptase or protease genes. It has been demonstrated that the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in combination or alternation

with a second, and perhaps third, antiviral compound that induces a different mutation(s) from that selected for by the principle drug. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus. In the case of administering the antiviral compounds in alternation, i.e. sequentially, the time gap between administering the first compound and the second compound is preferably not too long in order to achieve a beneficial effect. Preferably, the time gap is less than half a day, most preferably less than 6 hours.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation. The invention thus further provides a pharmaceutical formulation comprising a compound of the formula (I) and a compound of the formula (II) with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration in liquid or solid form or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound(s) with liquid carriers or finely divided solid carriers or both and then,

if necessary, shaping the product into the desired formulation.

Pharmaceutical formulation suitable for oral administration may conveniently be presented as discrete units such as capsules, including soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active ingredient(s); as a powder or granules; as a solution, a suspension or as an emulsion, for example as syrups, elixirs or self-emulsifying delivery systems (SEDDS). The active ingredient(s) may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The pharmaceutical composition according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient(s) may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for

constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound(s) with the softened or melted carrier(s) followed by chilling and shaping in moulds.

When desired the above described formulations adapted to give sustained release of the active ingredient(s) may be employed.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention are advantageous in the treatment and/or prophylaxis of viral infections in a patient, preferably human retrovirus (HRV) infections and hepatitis B, in particular HIV infections, especially multiresistant HIV infections. Therefore this invention may offer an aid especially for highly treatment experienced patients suffering from multiresistant HIV. In addition to the treatment of said diseases, the combinations, formulations and compositions according to this invention can be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HIV antibody or HIV-antigen positive or who have been exposed to HIV.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention may also be beneficial in preventing perinatal transmission of human retroviral (HRV) infections, in particular HIV-1, from mother to baby. According to this

method, a compound of the formula (I) and a compound of the formula (II), preferably 3'-deoxy-3'-fluorothymidine, and optionally further active compounds as described hereinbefore or hereinafter are administered in combination or alternation to the mother before giving birth.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention may also be beneficial in the treatment and/or prophylaxis of other HIV/AIDS-related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-related neurological conditions, anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections.

Therefore, patients to be treated would be especially those individuals:

1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum; and/or

2) in the case of HIV, having either a asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia, iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm^3 in the peripheral blood.

The pharmaceutical combination according to this invention can be tested for additive and synergistic activity against HIV according to a number of assays known in scientific and public literature, including the one described in the

WO 98/44913 and WO 00/51641, which are included herein by way of reference.

The present invention is illustrated in further detail by the following non-limiting examples of combinations according to this invention, comprising a 1st compound, a 2nd compound, optionally a 3rd compound, optionally a 4th compound and optionally a 5th compound. In the following tables the term "compound of the formula (I)" is abbreviated as "Cpd I".

Table 1 illustrating combinations of the compound of the formula (I), a compound of the formula (II) and one, two or more further NRTIs

1st compound	2nd compound	3rd compound	4th compound
Cpd I	FLT	Abacavir Sulfate	
Cpd I	FLT	Didanosine	
Cpd I	FLT	Emtricitabine	
Cpd I	FLT	Lamivudine	
Cpd I	FLT	Stavudine	
Cpd I	FLT	Tenofovir disoproxil fumarate	
Cpd I	FLT	Zalcitabine	
Cpd I	FLT	Zidovudine	
Cpd I	FLT	Amdoxovir	
Cpd I	FLT	Elvucitabine	
Cpd I	FLT	GS-7340	
Cpd I	FLT	INK-20	

Cpd I	FLT	MIV-210	
Cpd I	FLT	Racivir	
Cpd I	FLT	Reverset	
Cpd I	FLT	SPD-754	
Cpd I	FLT	BCH-13520	
Cpd I	FLT	BCH-10618	
Cpd I	FLG	Abacavir Sulfate	
Cpd I	FLG	Didanosine	
Cpd I	FLG	Emtricitabine	
Cpd I	FLG	Lamivudine	
Cpd I	FLG	Stavudine	
Cpd I	FLG	Tenofovir disoproxil fumarate	
Cpd I	FLG	Zalcitabine	
Cpd I	FLG	Zidovudine	
Cpd I	FLG	Amdoxovir	
Cpd I	FLG	Elvucitabine	
Cpd I	FLG	GS-7340	
Cpd I	FLG	INK-20	
Cpd I	FLG	MIV-310	
Cpd I	FLG	Racivir	
Cpd I	FLG	Reverset	
Cpd I	FLG	SPD-754	
Cpd I	FLG	BCH-13520	
Cpd I	FLG	BCH-10618	

Cpd I	FLT	Ritonavir	Abacavir Sulfate
Cpd I	FLT	Ritonavir	Didanosine
Cpd I	FLT	Ritonavir	Emtricitabine
Cpd I	FLT	Ritonavir	Lamivudine
Cpd I	FLT	Ritonavir	Stavudine
Cpd I	FLT	Ritonavir	Tenofovir disoproxil fumarate
Cpd I	FLT	Ritonavir	Zalcitabine
Cpd I	FLT	Ritonavir	Zidovudine
Cpd I	FLT	Ritonavir	Amdoxovir
Cpd I	FLT	Ritonavir	Elvucitabine
Cpd I	FLT	Ritonavir	GS-7340
Cpd I	FLT	Ritonavir	INK-20
Cpd I	FLT	Ritonavir	MIV-210
Cpd I	FLT	Ritonavir	Racivir
Cpd I	FLT	Ritonavir	Reverset
Cpd I	FLT	Ritonavir	SPD-754
Cpd I	FLT	Ritonavir	BCH-13520
Cpd I	FLT	Ritonavir	BCH-10618
Cpd I	FLG	Ritonavir	Abacavir Sulfate
Cpd I	FLG	Ritonavir	Didanosine
Cpd I	FLG	Ritonavir	Emtricitabine
Cpd I	FLG	Ritonavir	Lamivudine
Cpd I	FLG	Ritonavir	Stavudine

Cpd I	FLG	Ritonavir	Tenofovir disoproxil fumarate
Cpd I	FLG	Ritonavir	Zalcitabine
Cpd I	FLG	Ritonavir	Zidovudine
Cpd I	FLG	Ritonavir	Amdoxovir
Cpd I	FLG	Ritonavir	Elvucitabine
Cpd I	FLG	Ritonavir	GS-7340
Cpd I	FLG	Ritonavir	INK-20
Cpd I	FLG	Ritonavir	MIV-310
Cpd I	FLG	Ritonavir	Racivir
Cpd I	FLG	Ritonavir	Reverset
Cpd I	FLG	Ritonavir	SPD-754
Cpd I	FLG	Ritonavir	BCH-13520
Cpd I	FLG	Ritonavir	BCH-10618

Table 2 illustrating combinations of the compound of the formula (I), a compound of the formula (II), a protease inhibitor and optionally one, two or more further NRTIs

1st compound	2nd compound	3rd compound	4th compound
Cpd I	FLT	Amprenavir	
Cpd I	FLT	Atazanavir	
Cpd I	FLT	Indinavir Sulfate	
Cpd I	FLT	Lexiva	
Cpd I	FLT	Lopinavir + Ritonavir	

Cpd I	FLT	Nelfinavir Mesylate	
Cpd I	FLT	Ritonavir	
Cpd I	FLT	Saquinavir	
Cpd I	FLT	Tipranavir + Ritonavir	
Cpd I	FLT	AG-1776	
Cpd I	FLT	AG-1859	
Cpd I	FLT	DPC-681/684	
Cpd I	FLT	GS224338	
Cpd I	FLT	KNI-272	
Cpd I	FLT	Nar-DG-35	
Cpd I	FLT	P(PL)-100	
Cpd I	FLT	P-1946	
Cpd I	FLT	R-944	
Cpd I	FLT	RO-0334649	
Cpd I	FLT	TMC-114	
Cpd I	FLT	VX-385	
Cpd I	FLT	VX-478	
Cpd I	FLG	Amprenavir	
Cpd I	FLG	Atazanavir	
Cpd I	FLG	Indinavir Sulfate	
Cpd I	FLG	Lexiva	
Cpd I	FLG	Lopinavir + Ritonavir	
Cpd I	FLG	Nelfinavir	

		Mesylate	
Cpd I	FLG	Ritonavir	
Cpd I	FLG	Saquinavir	
Cpd I	FLG	Tipranavir + Ritonavir	
Cpd I	FLG	AG-1776	
Cpd I	FLG	AG-1859	
Cpd I	FLG	DPC-681/684	
Cpd I	FLG	GS224338	
Cpd I	FLG	KNI-272	
Cpd I	FLG	Nar-DG-35	
Cpd I	FLG	P(PL)-100	
Cpd I	FLG	P-1946	
Cpd I	FLG	R-944	
Cpd I	FLG	RO-0334649	
Cpd I	FLG	TMC-114	
Cpd I	FLG	VX-385	
Cpd I	FLG	VX-478	
Cpd I	FLT	Ritonavir	Amprenavir
Cpd I	FLT	Ritonavir	Atazanavir
Cpd I	FLT	Ritonavir	Indinavir Sulfate
Cpd I	FLT	Ritonavir	Lexiva
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate
Cpd I	FLT	Ritonavir	Saquinavir
Cpd I	FLT	Ritonavir	AG-1776

Cpd I	FLT	Ritonavir	AG-1859
Cpd I	FLT	Ritonavir	DPC-681/684
Cpd I	FLT	Ritonavir	GS224338
Cpd I	FLT	Ritonavir	KNI-272
Cpd I	FLT	Ritonavir	Nar-DG-35
Cpd I	FLT	Ritonavir	P(PL)-100
Cpd I	FLT	Ritonavir	P-1946
Cpd I	FLT	Ritonavir	R-944
Cpd I	FLT	Ritonavir	RO-0334649
Cpd I	FLT	Ritonavir	TMC-114
Cpd I	FLT	Ritonavir	VX-385
Cpd I	FLT	Ritonavir	VX-478
Cpd I	FLG	Ritonavir	Amprenavir
Cpd I	FLG	Ritonavir	Atazanavir
Cpd I	FLG	Ritonavir	Indinavir Sulfate
Cpd I	FLG	Ritonavir	Lexiva
Cpd I	FLG	Ritonavir	Lopinavir
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate
Cpd I	FLG	Ritonavir	Ritonavir
Cpd I	FLG	Ritonavir	Saquinavir
Cpd I	FLG	Ritonavir	Tipranavir
Cpd I	FLG	Ritonavir	AG-1776
Cpd I	FLG	Ritonavir	AG-1859
Cpd I	FLG	Ritonavir	DPC-681/684

Cpd I	FLG	Ritonavir	GS224338
Cpd I	FLG	Ritonavir	KNI-272
Cpd I	FLG	Ritonavir	Nar-DG-35
Cpd I	FLG	Ritonavir	P(PL)-100
Cpd I	FLG	Ritonavir	P-1946
Cpd I	FLG	Ritonavir	R-944
Cpd I	FLG	Ritonavir	RO-0334649
Cpd I	FLG	Ritonavir	TMC-114
Cpd I	FLG	Ritonavir	VX-385
Cpd I	FLG	Ritonavir	VX-478

Table 3 illustrating combinations of the compound of the formula (I), a compound of the formula (II), an entry inhibitor and optionally one, two or more further NRTIs

1st compound	2nd compound	3rd compound	4th compound
Cpd I	FLT	Enfurvirtide	
Cpd I	FLT	T-1249	
Cpd I	FLT	AMD-070	
Cpd I	FLT	BlockAide/CR	
Cpd I	FLT	BMS 806	
Cpd I	FLT	KRH-1636	
Cpd I	FLT	ONO-4128	
Cpd I	FLT	Pro-140	
Cpd I	FLT	PRO-542	
Cpd I	FLT	SCH-D	
Cpd I	FLT	TAK-220	

Cpd I	FLT	TNX-355	
Cpd I	FLT	UK-427,857	
Cpd I	FLG	Enfurvirtide	
Cpd I	FLG	T-1249	
Cpd I	FLG	AMD-070	
Cpd I	FLG	BlockAide/CR	
Cpd I	FLG	BMS 806	
Cpd I	FLG	KRH-1636	
Cpd I	FLG	ONO-4128	
Cpd I	FLG	Pro-140	
Cpd I	FLG	PRO-542	
Cpd I	FLG	SCH-D	
Cpd I	FLG	TAK-220	
Cpd I	FLG	TNX-355	
Cpd I	FLG	UK-427,857	
Cpd I	FLT	Ritonavir	Enfurvirtide
Cpd I	FLT	Ritonavir	T-1249
Cpd I	FLT	Ritonavir	AMD-070
Cpd I	FLT	Ritonavir	BlockAide/CR
Cpd I	FLT	Ritonavir	BMS 806
Cpd I	FLT	Ritonavir	KRH-1636
Cpd I	FLT	Ritonavir	ONO-4128
Cpd I	FLT	Ritonavir	Pro-140
Cpd I	FLT	Ritonavir	PRO-542
Cpd I	FLT	Ritonavir	SCH-D
Cpd I	FLT	Ritonavir	TAK-220

Cpd I	FLT	Ritonavir	TNX-355
Cpd I	FLT	Ritonavir	UK-427,857
Cpd I	FLG	Ritonavir	Enfurvirtide
Cpd I	FLG	Ritonavir	T-1249
Cpd I	FLG	Ritonavir	AMD-070
Cpd I	FLG	Ritonavir	BlockAide/CR
Cpd I	FLG	Ritonavir	BMS 806
Cpd I	FLG	Ritonavir	KRH-1636
Cpd I	FLG	Ritonavir	ONO-4128
Cpd I	FLG	Ritonavir	Pro-140
Cpd I	FLG	Ritonavir	PRO-542
Cpd I	FLG	Ritonavir	SCH-D
Cpd I	FLG	Ritonavir	TAK-220
Cpd I	FLG	Ritonavir	TNX-355
Cpd I	FLG	Ritonavir	UK-427,857

Table 4 illustrating combinations of the compound of the formula (I), a compound of the formula (II), a protease inhibitor, an entry inhibitor and optionally one, two or more further NRTIs

1st compound	2nd compound	3rd compound	4th compound	5th compound
Cpd I	FLT	Amprenavir	Enfurvirtide	
Cpd I	FLT	Amprenavir	T-1249	
Cpd I	FLT	Amprenavir	AMD-070	
Cpd I	FLT	Amprenavir	BlockAide/CR	

Cpd I	FLT	Amprenavir	BMS 806	
Cpd I	FLT	Amprenavir	KRH-1636	
Cpd I	FLT	Amprenavir	ONO-4128	
Cpd I	FLT	Amprenavir	Pro-140	
Cpd I	FLT	Amprenavir	PRO-542	
Cpd I	FLT	Amprenavir	SCH-D	
Cpd I	FLT	Amprenavir	TAK-220	
Cpd I	FLT	Amprenavir	TNX-355	
Cpd I	FLT	Amprenavir	UK-427,857	
Cpd I	FLT	Atazanavir	Enfurvirtide	
Cpd I	FLT	Atazanavir	T-1249	
Cpd I	FLT	Atazanavir	AMD-070	
Cpd I	FLT	Atazanavir	BlockAide/CR	
Cpd I	FLT	Atazanavir	BMS 806	
Cpd I	FLT	Atazanavir	KRH-1636	
Cpd I	FLT	Atazanavir	ONO-4128	
Cpd I	FLT	Atazanavir	Pro-140	
Cpd I	FLT	Atazanavir	PRO-542	
Cpd I	FLT	Atazanavir	SCH-D	
Cpd I	FLT	Atazanavir	TAK-220	
Cpd I	FLT	Atazanavir	TNX-355	
Cpd I	FLT	Atazanavir	UK-427,857	
Cpd I	FLT	Indinavir Sulfate	Enfurvirtide	
Cpd I	FLT	Indinavir Sulfate	T-1249	

Cpd I	FLT	Indinavir Sulfate	AMD-070	
Cpd I	FLT	Indinavir Sulfate	BlockAide/CR	
Cpd I	FLT	Indinavir Sulfate	BMS 806	
Cpd I	FLT	Indinavir Sulfate	KRH-1636	
Cpd I	FLT	Indinavir Sulfate	ONO-4128	
Cpd I	FLT	Indinavir Sulfate	Pro-140	
Cpd I	FLT	Indinavir Sulfate	PRO-542	
Cpd I	FLT	Indinavir Sulfate	SCH-D	
Cpd I	FLT	Indinavir Sulfate	TAK-220	
Cpd I	FLT	Indinavir Sulfate	TNX-355	
Cpd I	FLT	Indinavir Sulfate	UK-427,857	
Cpd I	FLT	Lexiva	Enfurvirtide	
Cpd I	FLT	Lexiva	T-1249	
Cpd I	FLT	Lexiva	AMD-070	
Cpd I	FLT	Lexiva	BlockAide/CR	
Cpd I	FLT	Lexiva	BMS 806	
Cpd I	FLT	Lexiva	KRH-1636	
Cpd I	FLT	Lexiva	ONO-4128	

Cpd I	FLT	Lexiva	Pro-140	
Cpd I	FLT	Lexiva	PRO-542	
Cpd I	FLT	Lexiva	SCH-D	
Cpd I	FLT	Lexiva	TAK-220	
Cpd I	FLT	Lexiva	TNX-355	
Cpd I	FLT	Lexiva	UK-427,857	
Cpd I	FLT	Lopinavir	Enfurvirtide	
Cpd I	FLT	Lopinavir	T-1249	
Cpd I	FLT	Lopinavir	AMD-070	
Cpd I	FLT	Lopinavir	BlockAide/CR	
Cpd I	FLT	Lopinavir	BMS 806	
Cpd I	FLT	Lopinavir	KRH-1636	
Cpd I	FLT	Lopinavir	ONO-4128	
Cpd I	FLT	Lopinavir	Pro-140	
Cpd I	FLT	Lopinavir	PRO-542	
Cpd I	FLT	Lopinavir	SCH-D	
Cpd I	FLT	Lopinavir	TAK-220	
Cpd I	FLT	Lopinavir	TNX-355	
Cpd I	FLT	Lopinavir	UK-427,857	
Cpd I	FLT	Nelfinavir Mesylate	Enfurvirtide	
Cpd I	FLT	Nelfinavir Mesylate	T-1249	
Cpd I	FLT	Nelfinavir Mesylate	AMD-070	
Cpd I	FLT	Nelfinavir Mesylate	BlockAide/CR	

Cpd I	FLT	Nelfinavir Mesylate	BMS 806	
Cpd I	FLT	Nelfinavir Mesylate	KRH-1636	
Cpd I	FLT	Nelfinavir Mesylate	ONO-4128	
Cpd I	FLT	Nelfinavir Mesylate	Pro-140	
Cpd I	FLT	Nelfinavir Mesylate	PRO-542	
Cpd I	FLT	Nelfinavir Mesylate	SCH-D	
Cpd I	FLT	Nelfinavir Mesylate	TAK-220	
Cpd I	FLT	Nelfinavir Mesylate	TNX-355	
Cpd I	FLT	Nelfinavir Mesylate	UK-427,857	
Cpd I	FLT	Ritonavir	Enfurvirtide	
Cpd I	FLT	Ritonavir	T-1249	
Cpd I	FLT	Ritonavir	AMD-070	
Cpd I	FLT	Ritonavir	BlockAide/CR	
Cpd I	FLT	Ritonavir	BMS 806	
Cpd I	FLT	Ritonavir	KRH-1636	
Cpd I	FLT	Ritonavir	ONO-4128	
Cpd I	FLT	Ritonavir	Pro-140	
Cpd I	FLT	Ritonavir	PRO-542	
Cpd I	FLT	Ritonavir	SCH-D	

Cpd I	FLT	Ritonavir	TAK-220	
Cpd I	FLT	Ritonavir	TNX-355	
Cpd I	FLT	Ritonavir	UK-427,857	
Cpd I	FLT	Saquinavir	Enfurvirtide	
Cpd I	FLT	Saquinavir	T-1249	
Cpd I	FLT	Saquinavir	AMD-070	
Cpd I	FLT	Saquinavir	BlockAide/CR	
Cpd I	FLT	Saquinavir	BMS 806	
Cpd I	FLT	Saquinavir	KRH-1636	
Cpd I	FLT	Saquinavir	ONO-4128	
Cpd I	FLT	Saquinavir	Pro-140	
Cpd I	FLT	Saquinavir	PRO-542	
Cpd I	FLT	Saquinavir	SCH-D	
Cpd I	FLT	Saquinavir	TAK-220	
Cpd I	FLT	Saquinavir	TNX-355	
Cpd I	FLT	Saquinavir	UK-427,857	
Cpd I	FLT	Tipranavir	Enfurvirtide	
Cpd I	FLT	Tipranavir	T-1249	
Cpd I	FLT	Tipranavir	AMD-070	
Cpd I	FLT	Tipranavir	BlockAide/CR	
Cpd I	FLT	Tipranavir	BMS 806	
Cpd I	FLT	Tipranavir	KRH-1636	
Cpd I	FLT	Tipranavir	ONO-4128	
Cpd I	FLT	Tipranavir	Pro-140	
Cpd I	FLT	Tipranavir	PRO-542	
Cpd I	FLT	Tipranavir	SCH-D	

Cpd I	FLT	Tipranavir	TAK-220	
Cpd I	FLT	Tipranavir	TNX-355	
Cpd I	FLT	Tipranavir	UK-427,857	
Cpd I	FLG	Amprenavir	Enfurvirtide	
Cpd I	FLG	Amprenavir	T-1249	
Cpd I	FLG	Amprenavir	AMD-070	
Cpd I	FLG	Amprenavir	BlockAide/CR	
Cpd I	FLG	Amprenavir	BMS 806	
Cpd I	FLG	Amprenavir	KRH-1636	
Cpd I	FLG	Amprenavir	ONO-4128	
Cpd I	FLG	Amprenavir	Pro-140	
Cpd I	FLG	Amprenavir	PRO-542	
Cpd I	FLG	Amprenavir	SCH-D	
Cpd I	FLG	Amprenavir	TAK-220	
Cpd I	FLG	Amprenavir	TNX-355	
Cpd I	FLG	Amprenavir	UK-427,857	
Cpd I	FLG	Atazanavir	Enfurvirtide	
Cpd I	FLG	Atazanavir	T-1249	
Cpd I	FLG	Atazanavir	AMD-070	
Cpd I	FLG	Atazanavir	BlockAide/CR	
Cpd I	FLG	Atazanavir	BMS 806	
Cpd I	FLG	Atazanavir	KRH-1636	
Cpd I	FLG	Atazanavir	ONO-4128	
Cpd I	FLG	Atazanavir	Pro-140	
Cpd I	FLG	Atazanavir	PRO-542	
Cpd I	FLG	Atazanavir	SCH-D	

Cpd I	FLG	Atazanavir	TAK-220	
Cpd I	FLG	Atazanavir	TNX-355	
Cpd I	FLG	Atazanavir	UK-427,857	
Cpd I	FLG	Indinavir Sulfate	Enfurvirtide	
Cpd I	FLG	Indinavir Sulfate	T-1249	
Cpd I	FLG	Indinavir Sulfate	AMD-070	
Cpd I	FLG	Indinavir Sulfate	BlockAide/CR	
Cpd I	FLG	Indinavir Sulfate	BMS 806	
Cpd I	FLG	Indinavir Sulfate	KRH-1636	
Cpd I	FLG	Indinavir Sulfate	ONO-4128	
Cpd I	FLG	Indinavir Sulfate	Pro-140	
Cpd I	FLG	Indinavir Sulfate	PRO-542	
Cpd I	FLG	Indinavir Sulfate	SCH-D	
Cpd I	FLG	Indinavir Sulfate	TAK-220	
Cpd I	FLG	Indinavir Sulfate	TNX-355	
Cpd I	FLG	Indinavir Sulfate	UK-427,857	

Cpd I	FLG	Lexiva	Enfurvirtide	
Cpd I	FLG	Lexiva	T-1249	
Cpd I	FLG	Lexiva	AMD-070	
Cpd I	FLG	Lexiva	BlockAide/CR	
Cpd I	FLG	Lexiva	BMS 806	
Cpd I	FLG	Lexiva	KRH-1636	
Cpd I	FLG	Lexiva	ONO-4128	
Cpd I	FLG	Lexiva	Pro-140	
Cpd I	FLG	Lexiva	PRO-542	
Cpd I	FLG	Lexiva	SCH-D	
Cpd I	FLG	Lexiva	TAK-220	
Cpd I	FLG	Lexiva	TNX-355	
Cpd I	FLG	Lexiva	UK-427,857	
Cpd I	FLG	Lopinavir	Enfurvirtide	
Cpd I	FLG	Lopinavir	T-1249	
Cpd I	FLG	Lopinavir	AMD-070	
Cpd I	FLG	Lopinavir	BlockAide/CR	
Cpd I	FLG	Lopinavir	BMS 806	
Cpd I	FLG	Lopinavir	KRH-1636	
Cpd I	FLG	Lopinavir	ONO-4128	
Cpd I	FLG	Lopinavir	Pro-140	
Cpd I	FLG	Lopinavir	PRO-542	
Cpd I	FLG	Lopinavir	SCH-D	
Cpd I	FLG	Lopinavir	TAK-220	
Cpd I	FLG	Lopinavir	TNX-355	
Cpd I	FLG	Lopinavir	UK-427,857	

Cpd I	FLG	Nelfinavir Mesylate	Enfurvirtide	
Cpd I	FLG	Nelfinavir Mesylate	T-1249	
Cpd I	FLG	Nelfinavir Mesylate	AMD-070	
Cpd I	FLG	Nelfinavir Mesylate	BlockAide/CR	
Cpd I	FLG	Nelfinavir Mesylate	BMS 806	
Cpd I	FLG	Nelfinavir Mesylate	KRH-1636	
Cpd I	FLG	Nelfinavir Mesylate	ONO-4128	
Cpd I	FLG	Nelfinavir Mesylate	Pro-140	
Cpd I	FLG	Nelfinavir Mesylate	PRO-542	
Cpd I	FLG	Nelfinavir Mesylate	SCH-D	
Cpd I	FLG	Nelfinavir Mesylate	TAK-220	
Cpd I	FLG	Nelfinavir Mesylate	TNX-355	
Cpd I	FLG	Nelfinavir Mesylate	UK-427,857	
Cpd I	FLG	Ritonavir	Enfurvirtide	
Cpd I	FLG	Ritonavir	T-1249	
Cpd I	FLG	Ritonavir	AMD-070	

Cpd I	FLG	Ritonavir	BlockAide/CR	
Cpd I	FLG	Ritonavir	BMS 806	
Cpd I	FLG	Ritonavir	KRH-1636	
Cpd I	FLG	Ritonavir	ONO-4128	
Cpd I	FLG	Ritonavir	Pro-140	
Cpd I	FLG	Ritonavir	PRO-542	
Cpd I	FLG	Ritonavir	SCH-D	
Cpd I	FLG	Ritonavir	TAK-220	
Cpd I	FLG	Ritonavir	TNX-355	
Cpd I	FLG	Ritonavir	UK-427,857	
Cpd I	FLG	Saquinavir	Enfurvirtide	
Cpd I	FLG	Saquinavir	T-1249	
Cpd I	FLG	Saquinavir	AMD-070	
Cpd I	FLG	Saquinavir	BlockAide/CR	
Cpd I	FLG	Saquinavir	BMS 806	
Cpd I	FLG	Saquinavir	KRH-1636	
Cpd I	FLG	Saquinavir	ONO-4128	
Cpd I	FLG	Saquinavir	Pro-140	
Cpd I	FLG	Saquinavir	PRO-542	
Cpd I	FLG	Saquinavir	SCH-D	
Cpd I	FLG	Saquinavir	TAK-220	
Cpd I	FLG	Saquinavir	TNX-355	
Cpd I	FLG	Saquinavir	UK-427,857	
Cpd I	FLG	Tipranavir	Enfurvirtide	
Cpd I	FLG	Tipranavir	T-1249	
Cpd I	FLG	Tipranavir	AMD-070	

Cpd I	FLG	Tipranavir	BlockAide/CR	
Cpd I	FLG	Tipranavir	BMS 806	
Cpd I	FLG	Tipranavir	KRH-1636	
Cpd I	FLG	Tipranavir	ONO-4128	
Cpd I	FLG	Tipranavir	Pro-140	
Cpd I	FLG	Tipranavir	PRO-542	
Cpd I	FLG	Tipranavir	SCH-D	
Cpd I	FLG	Tipranavir	TAK-220	
Cpd I	FLG	Tipranavir	TNX-355	
Cpd I	FLG	Tipranavir	UK-427,857	
Cpd I	FLT	Ritonavir	Amprenavir	Enfurvirtide
Cpd I	FLT	Ritonavir	Amprenavir	T-1249
Cpd I	FLT	Ritonavir	Amprenavir	AMD-070
Cpd I	FLT	Ritonavir	Amprenavir	BlockAide/CR
Cpd I	FLT	Ritonavir	Amprenavir	BMS 806
Cpd I	FLT	Ritonavir	Amprenavir	KRH-1636
Cpd I	FLT	Ritonavir	Amprenavir	ONO-4128
Cpd I	FLT	Ritonavir	Amprenavir	Pro-140
Cpd I	FLT	Ritonavir	Amprenavir	PRO-542
Cpd I	FLT	Ritonavir	Amprenavir	SCH-D
Cpd I	FLT	Ritonavir	Amprenavir	TAK-220
Cpd I	FLT	Ritonavir	Amprenavir	TNX-355
Cpd I	FLT	Ritonavir	Amprenavir	UK-427,857
Cpd I	FLT	Ritonavir	Atazanavir	Enfurvirtide
Cpd I	FLT	Ritonavir	Atazanavir	T-1249
Cpd I	FLT	Ritonavir	Atazanavir	AMD-070

Cpd I	FLT	Ritonavir	Atazanavir	BlockAide/CR
Cpd I	FLT	Ritonavir	Atazanavir	BMS 806
Cpd I	FLT	Ritonavir	Atazanavir	KRH-1636
Cpd I	FLT	Ritonavir	Atazanavir	ONO-4128
Cpd I	FLT	Ritonavir	Atazanavir	Pro-140
Cpd I	FLT	Ritonavir	Atazanavir	PRO-542
Cpd I	FLT	Ritonavir	Atazanavir	SCH-D
Cpd I	FLT	Ritonavir	Atazanavir	TAK-220
Cpd I	FLT	Ritonavir	Atazanavir	TNX-355
Cpd I	FLT	Ritonavir	Atazanavir	UK-427,857
Cpd I	FLT	Ritonavir	Indinavir Sulfate	Enfurvirtide
Cpd I	FLT	Ritonavir	Indinavir Sulfate	T-1249
Cpd I	FLT	Ritonavir	Indinavir Sulfate	AMD-070
Cpd I	FLT	Ritonavir	Indinavir Sulfate	BlockAide/CR
Cpd I	FLT	Ritonavir	Indinavir Sulfate	BMS 806
Cpd I	FLT	Ritonavir	Indinavir Sulfate	KRH-1636
Cpd I	FLT	Ritonavir	Indinavir Sulfate	ONO-4128
Cpd I	FLT	Ritonavir	Indinavir Sulfate	Pro-140
Cpd I	FLT	Ritonavir	Indinavir Sulfate	PRO-542

Cpd I	FLT	Ritonavir	Indinavir Sulfate	SCH-D
Cpd I	FLT	Ritonavir	Indinavir Sulfate	TAK-220
Cpd I	FLT	Ritonavir	Indinavir Sulfate	TNX-355
Cpd I	FLT	Ritonavir	Indinavir Sulfate	UK-427,857
Cpd I	FLT	Ritonavir	Lexiva	Enfurvirtide
Cpd I	FLT	Ritonavir	Lexiva	T-1249
Cpd I	FLT	Ritonavir	Lexiva	AMD-070
Cpd I	FLT	Ritonavir	Lexiva	BlockAide/CR
Cpd I	FLT	Ritonavir	Lexiva	BMS 806
Cpd I	FLT	Ritonavir	Lexiva	KRH-1636
Cpd I	FLT	Ritonavir	Lexiva	ONO-4128
Cpd I	FLT	Ritonavir	Lexiva	Pro-140
Cpd I	FLT	Ritonavir	Lexiva	PRO-542
Cpd I	FLT	Ritonavir	Lexiva	SCH-D
Cpd I	FLT	Ritonavir	Lexiva	TAK-220
Cpd I	FLT	Ritonavir	Lexiva	TNX-355
Cpd I	FLT	Ritonavir	Lexiva	UK-427,857
Cpd I	FLT	Ritonavir	Lopinavir	Enfurvirtide
Cpd I	FLT	Ritonavir	Lopinavir	T-1249
Cpd I	FLT	Ritonavir	Lopinavir	AMD-070
Cpd I	FLT	Ritonavir	Lopinavir	BlockAide/CR
Cpd I	FLT	Ritonavir	Lopinavir	BMS 806
Cpd I	FLT	Ritonavir	Lopinavir	KRH-1636

Cpd I	FLT	Ritonavir	Lopinavir	ONO-4128
Cpd I	FLT	Ritonavir	Lopinavir	Pro-140
Cpd I	FLT	Ritonavir	Lopinavir	PRO-542
Cpd I	FLT	Ritonavir	Lopinavir	SCH-D
Cpd I	FLT	Ritonavir	Lopinavir	TAK-220
Cpd I	FLT	Ritonavir	Lopinavir	TNX-355
Cpd I	FLT	Ritonavir	Lopinavir	UK-427,857
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	Enfurvirtide
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	T-1249
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	AMD-070
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	BlockAide/CR
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	BMS 806
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	KRH-1636
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	ONO-4128
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	Pro-140
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	PRO-542
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	SCH-D
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	TAK-220

Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	TNX-355
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	UK-427,857
Cpd I	FLT	Ritonavir	Saquinavir	Enfurvirtide
Cpd I	FLT	Ritonavir	Saquinavir	T-1249
Cpd I	FLT	Ritonavir	Saquinavir	AMD-070
Cpd I	FLT	Ritonavir	Saquinavir	BlockAide/CR
Cpd I	FLT	Ritonavir	Saquinavir	BMS 806
Cpd I	FLT	Ritonavir	Saquinavir	KRH-1636
Cpd I	FLT	Ritonavir	Saquinavir	ONO-4128
Cpd I	FLT	Ritonavir	Saquinavir	Pro-140
Cpd I	FLT	Ritonavir	Saquinavir	PRO-542
Cpd I	FLT	Ritonavir	Saquinavir	SCH-D
Cpd I	FLT	Ritonavir	Saquinavir	TAK-220
Cpd I	FLT	Ritonavir	Saquinavir	TNX-355
Cpd I	FLT	Ritonavir	Saquinavir	UK-427,857
Cpd I	FLT	Ritonavir	Tipranavir	Enfurvirtide
Cpd I	FLT	Ritonavir	Tipranavir	T-1249
Cpd I	FLT	Ritonavir	Tipranavir	AMD-070
Cpd I	FLT	Ritonavir	Tipranavir	BlockAide/CR
Cpd I	FLT	Ritonavir	Tipranavir	BMS 806
Cpd I	FLT	Ritonavir	Tipranavir	KRH-1636
Cpd I	FLT	Ritonavir	Tipranavir	ONO-4128
Cpd I	FLT	Ritonavir	Tipranavir	Pro-140
Cpd I	FLT	Ritonavir	Tipranavir	PRO-542

Cpd I	FLT	Ritonavir	Tipranavir	SCH-D
Cpd I	FLT	Ritonavir	Tipranavir	TAK-220
Cpd I	FLT	Ritonavir	Tipranavir	TNX-355
Cpd I	FLT	Ritonavir	Tipranavir	UK-427,857
Cpd I	FLG	Ritonavir	Amprenavir	Enfurvirtide
Cpd I	FLG	Ritonavir	Amprenavir	T-1249
Cpd I	FLG	Ritonavir	Amprenavir	AMD-070
Cpd I	FLG	Ritonavir	Amprenavir	BlockAide/CR
Cpd I	FLG	Ritonavir	Amprenavir	BMS 806
Cpd I	FLG	Ritonavir	Amprenavir	KRH-1636
Cpd I	FLG	Ritonavir	Amprenavir	ONO-4128
Cpd I	FLG	Ritonavir	Amprenavir	Pro-140
Cpd I	FLG	Ritonavir	Amprenavir	PRO-542
Cpd I	FLG	Ritonavir	Amprenavir	SCH-D
Cpd I	FLG	Ritonavir	Amprenavir	TAK-220
Cpd I	FLG	Ritonavir	Amprenavir	TNX-355
Cpd I	FLG	Ritonavir	Amprenavir	UK-427,857
Cpd I	FLG	Ritonavir	Atazanavir	Enfurvirtide
Cpd I	FLG	Ritonavir	Atazanavir	T-1249
Cpd I	FLG	Ritonavir	Atazanavir	AMD-070
Cpd I	FLG	Ritonavir	Atazanavir	BlockAide/CR
Cpd I	FLG	Ritonavir	Atazanavir	BMS 806
Cpd I	FLG	Ritonavir	Atazanavir	KRH-1636
Cpd I	FLG	Ritonavir	Atazanavir	ONO-4128
Cpd I	FLG	Ritonavir	Atazanavir	Pro-140
Cpd I	FLG	Ritonavir	Atazanavir	PRO-542

Cpd I	FLG	Ritonavir	Atazanavir	SCH-D
Cpd I	FLG	Ritonavir	Atazanavir	TAK-220
Cpd I	FLG	Ritonavir	Atazanavir	TNX-355
Cpd I	FLG	Ritonavir	Atazanavir	UK-427,857
Cpd I	FLG	Ritonavir	Indinavir Sulfate	Enfurvirtide
Cpd I	FLG	Ritonavir	Indinavir Sulfate	T-1249
Cpd I	FLG	Ritonavir	Indinavir Sulfate	AMD-070
Cpd I	FLG	Ritonavir	Indinavir Sulfate	BlockAide/CR
Cpd I	FLG	Ritonavir	Indinavir Sulfate	BMS 806
Cpd I	FLG	Ritonavir	Indinavir Sulfate	KRH-1636
Cpd I	FLG	Ritonavir	Indinavir Sulfate	ONO-4128
Cpd I	FLG	Ritonavir	Indinavir Sulfate	Pro-140
Cpd I	FLG	Ritonavir	Indinavir Sulfate	PRO-542
Cpd I	FLG	Ritonavir	Indinavir Sulfate	SCH-D
Cpd I	FLG	Ritonavir	Indinavir Sulfate	TAK-220
Cpd I	FLG	Ritonavir	Indinavir Sulfate	TNX-355
Cpd I	FLG	Ritonavir	Indinavir	UK-427,857

			Sulfate	
Cpd I	FLG	Ritonavir	Lexiva	Enfurvirtide
Cpd I	FLG	Ritonavir	Lexiva	T-1249
Cpd I	FLG	Ritonavir	Lexiva	AMD-070
Cpd I	FLG	Ritonavir	Lexiva	BlockAide/CR
Cpd I	FLG	Ritonavir	Lexiva	BMS 806
Cpd I	FLG	Ritonavir	Lexiva	KRH-1636
Cpd I	FLG	Ritonavir	Lexiva	ONO-4128
Cpd I	FLG	Ritonavir	Lexiva	Pro-140
Cpd I	FLG	Ritonavir	Lexiva	PRO-542
Cpd I	FLG	Ritonavir	Lexiva	SCH-D
Cpd I	FLG	Ritonavir	Lexiva	TAK-220
Cpd I	FLG	Ritonavir	Lexiva	TNX-355
Cpd I	FLG	Ritonavir	Lexiva	UK-427,857
Cpd I	FLG	Ritonavir	Lopinavir	Enfurvirtide
Cpd I	FLG	Ritonavir	Lopinavir	T-1249
Cpd I	FLG	Ritonavir	Lopinavir	AMD-070
Cpd I	FLG	Ritonavir	Lopinavir	BlockAide/CR
Cpd I	FLG	Ritonavir	Lopinavir	BMS 806
Cpd I	FLG	Ritonavir	Lopinavir	KRH-1636
Cpd I	FLG	Ritonavir	Lopinavir	ONO-4128
Cpd I	FLG	Ritonavir	Lopinavir	Pro-140
Cpd I	FLG	Ritonavir	Lopinavir	PRO-542
Cpd I	FLG	Ritonavir	Lopinavir	SCH-D
Cpd I	FLG	Ritonavir	Lopinavir	TAK-220
Cpd I	FLG	Ritonavir	Lopinavir	TNX-355

Cpd I	FLG	Ritonavir	Lopinavir	UK-427,857
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	Enfurvirtide
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	T-1249
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	AMD-070
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	BlockAide/CR
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	BMS 806
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	KRH-1636
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	ONO-4128
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	Pro-140
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	PRO-542
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	SCH-D
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	TAK-220
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	TNX-355
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	UK-427,857
Cpd I	FLG	Ritonavir	Saquinavir	Enfurvirtide
Cpd I	FLG	Ritonavir	Saquinavir	T-1249

Cpd I	FLG	Ritonavir	Saquinavir	AMD-070
Cpd I	FLG	Ritonavir	Saquinavir	BlockAide/CR
Cpd I	FLG	Ritonavir	Saquinavir	BMS 806
Cpd I	FLG	Ritonavir	Saquinavir	KRH-1636
Cpd I	FLG	Ritonavir	Saquinavir	ONO-4128
Cpd I	FLG	Ritonavir	Saquinavir	Pro-140
Cpd I	FLG	Ritonavir	Saquinavir	PRO-542
Cpd I	FLG	Ritonavir	Saquinavir	SCH-D
Cpd I	FLG	Ritonavir	Saquinavir	TAK-220
Cpd I	FLG	Ritonavir	Saquinavir	TNX-355
Cpd I	FLG	Ritonavir	Saquinavir	UK-427,857
Cpd I	FLG	Ritonavir	Tipranavir	Enfurvirtide
Cpd I	FLG	Ritonavir	Tipranavir	T-1249
Cpd I	FLG	Ritonavir	Tipranavir	AMD-070
Cpd I	FLG	Ritonavir	Tipranavir	BlockAide/CR
Cpd I	FLG	Ritonavir	Tipranavir	BMS 806
Cpd I	FLG	Ritonavir	Tipranavir	KRH-1636
Cpd I	FLG	Ritonavir	Tipranavir	ONO-4128
Cpd I	FLG	Ritonavir	Tipranavir	Pro-140
Cpd I	FLG	Ritonavir	Tipranavir	PRO-542
Cpd I	FLG	Ritonavir	Tipranavir	SCH-D
Cpd I	FLG	Ritonavir	Tipranavir	TAK-220
Cpd I	FLG	Ritonavir	Tipranavir	TNX-355
Cpd I	FLG	Ritonavir	Tipranavir +	UK-427,857

Table 5 illustrating combinations of the compound of the formula (I), a compound of the formula (II), a protease inhibitor, an integrase inhibitor and optionally one, two or more further NRTIs

1st compound	2nd compound	3rd compound	3rd compound	4th compound
Cpd I	FLT	Amprenavir	L-870810	
Cpd I	FLT	Amprenavir	c-2507	
Cpd I	FLT	Amprenavir	S(RSC)-1838	
Cpd I	FLT	Atazanavir	L-870810	
Cpd I	FLT	Atazanavir	c-2507	
Cpd I	FLT	Atazanavir	S(RSC)-1838	
Cpd I	FLT	Indinavir Sulfate	c-2507	
Cpd I	FLT	Indinavir Sulfate	S(RSC)-1838	
Cpd I	FLT	Indinavir Sulfate	L-870810	
Cpd I	FLT	Lexiva	c-2507	
Cpd I	FLT	Lexiva	L-870810	
Cpd I	FLT	Lexiva	S(RSC)-1838	
Cpd I	FLT	Lopinavir	L-870810	
Cpd I	FLT	Lopinavir	c-2507	
Cpd I	FLT	Lopinavir	S(RSC)-1838	

Cpd I	FLT	Nelfinavir Mesylate	L-870810	
Cpd I	FLT	Nelfinavir Mesylate	c-2507	
Cpd I	FLT	Nelfinavir Mesylate	S(RSC)-1838	
Cpd I	FLT	Ritonavir	L-870810	
Cpd I	FLT	Ritonavir	c-2507	
Cpd I	FLT	Ritonavir	S(RSC)-1838	
Cpd I	FLT	Saquinavir	L-870810	
Cpd I	FLT	Saquinavir	c-2507	
Cpd I	FLT	Saquinavir	S(RSC)-1838	
Cpd I	FLT	Tipranavir	L-870810	
Cpd I	FLT	Tipranavir	c-2507	
Cpd I	FLT	Tipranavir	S(RSC)-1838	
Cpd I	FLG	Amprenavir	L-870810	
Cpd I	FLG	Amprenavir	c-2507	
Cpd I	FLG	Amprenavir	S(RSC)-1838	
Cpd I	FLG	Atazanavir	L-870810	
Cpd I	FLG	Atazanavir	c-2507	
Cpd I	FLG	Atazanavir	S(RSC)-1838	
Cpd I	FLG	Indinavir Sulfate	c-2507	

Cpd I	FLG	Indinavir Sulfate	S(RSC)-1838	
Cpd I	FLG	Indinavir Sulfate	L-870810	
Cpd I	FLG	Lexiva	c-2507	
Cpd I	FLG	Lexiva	L-870810	
Cpd I	FLG	Lexiva	S(RSC)-1838	
Cpd I	FLG	Lopinavir	L-870810	
Cpd I	FLG	Lopinavir	c-2507	
Cpd I	FLG	Lopinavir	S(RSC)-1838	
Cpd I	FLG	Nelfinavir Mesylate	L-870810	
Cpd I	FLG	Nelfinavir Mesylate	c-2507	
Cpd I	FLG	Nelfinavir Mesylate	S(RSC)-1838	
Cpd I	FLG	Ritonavir	L-870810	
Cpd I	FLG	Ritonavir	c-2507	
Cpd I	FLG	Ritonavir	S(RSC)-1838	
Cpd I	FLG	Saquinavir	L-870810	
Cpd I	FLG	Saquinavir	c-2507	
Cpd I	FLG	Saquinavir	S(RSC)-1838	
Cpd I	FLG	Tipranavir	L-870810	
Cpd I	FLG	Tipranavir	c-2507	

Cpd I	FLG	Tipranavir	S(RSC)-1838	
Cpd I	FLT	Ritonavir	Amprenavir	L-870810
Cpd I	FLT	Ritonavir	Amprenavir	c-2507
Cpd I	FLT	Ritonavir	Amprenavir	S(RSC)-1838
Cpd I	FLT	Ritonavir	Atazanavir	L-870810
Cpd I	FLT	Ritonavir	Atazanavir	c-2507
Cpd I	FLT	Ritonavir	Atazanavir	S(RSC)-1838
Cpd I	FLT	Ritonavir	Indinavir Sulfate	c-2507
Cpd I	FLT	Ritonavir	Indinavir Sulfate	S(RSC)-1838
Cpd I	FLT	Ritonavir	Indinavir Sulfate	L-870810
Cpd I	FLT	Ritonavir	Lexiva	c-2507
Cpd I	FLT	Ritonavir	Lexiva	L-870810
Cpd I	FLT	Ritonavir	Lexiva	S(RSC)-1838
Cpd I	FLT	Ritonavir	Lopinavir	L-870810
Cpd I	FLT	Ritonavir	Lopinavir	c-2507
Cpd I	FLT	Ritonavir	Lopinavir	S(RSC)-1838
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	L-870810
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	c-2507
Cpd I	FLT	Ritonavir	Nelfinavir Mesylate	S(RSC)-1838
Cpd I	FLT	Ritonavir	Saquinavir	L-870810

Cpd I	FLT	Ritonavir	Saquinavir	c-2507
Cpd I	FLT	Ritonavir	Saquinavir	S(RSC)-1838
Cpd I	FLT	Ritonavir	Tipranavir	L-870810
Cpd I	FLT	Ritonavir	Tipranavir	c-2507
Cpd I	FLT	Ritonavir	Tipranavir	S(RSC)-1838
Cpd I	FLG	Ritonavir	Amprenavir	L-870810
Cpd I	FLG	Ritonavir	Amprenavir	c-2507
Cpd I	FLG	Ritonavir	Amprenavir	S(RSC)-1838
Cpd I	FLG	Ritonavir	Atazanavir	L-870810
Cpd I	FLG	Ritonavir	Atazanavir	c-2507
Cpd I	FLG	Ritonavir	Atazanavir	S(RSC)-1838
Cpd I	FLG	Ritonavir	Indinavir Sulfate	c-2507
Cpd I	FLG	Ritonavir	Indinavir Sulfate	S(RSC)-1838
Cpd I	FLG	Ritonavir	Indinavir Sulfate	L-870810
Cpd I	FLG	Ritonavir	Lexiva	c-2507
Cpd I	FLG	Ritonavir	Lexiva	L-870810
Cpd I	FLG	Ritonavir	Lexiva	S(RSC)-1838
Cpd I	FLG	Ritonavir	Lopinavir	L-870810
Cpd I	FLG	Ritonavir	Lopinavir	c-2507
Cpd I	FLG	Ritonavir	Lopinavir	S(RSC)-1838
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	L-870810
Cpd I	FLG	Ritonavir	Nelfinavir	c-2507

			Mesylate	
Cpd I	FLG	Ritonavir	Nelfinavir Mesylate	S(RSC)-1838
Cpd I	FLG	Ritonavir	Saquinavir	L-870810
Cpd I	FLG	Ritonavir	Saquinavir	c-2507
Cpd I	FLG	Ritonavir	Saquinavir	S(RSC)-1838
Cpd I	FLG	Ritonavir	Tipranavir	L-870810
Cpd I	FLG	Ritonavir	Tipranavir	c-2507
Cpd I	FLG	Ritonavir	Tipranavir	S(RSC)-1838

Table 6 illustrating combinations of the compound of the formula (I), a compound of the formula (II) and a further antiviral

1st compound	2nd compound	3rd compound	4th compound
Cpd I	FLT	PA-457	
Cpd I	FLT	KPC-2	
Cpd I	FLT	HGTV-43	
Cpd I	FLT	Delavirdine	
Cpd I	FLT	Efavirenz	
Cpd I	FLT	Nevirapine	
Cpd I	FLT	(+)-Calanolide A or B	
Cpd I	FLT	Capravirine	
Cpd I	FLT	GW-695634	
Cpd I	FLT	MIV-150	

Cpd I	FLT	MV026048	
Cpd I	FLT	NV-05	
Cpd I	FLT	R-278474	
Cpd I	FLT	RS-1588	
Cpd I	FLT	TMC-120/125	
Cpd I	FLT	TMC-125	
Cpd I	FLT	UC-781	
Cpd I	FLT	YM-215389	
Cpd I	FLG	PA-457	
Cpd I	FLG	KPC-2	
Cpd I	FLG	HGTV-43	
Cpd I	FLG	Delavirdine	
Cpd I	FLG	Efavirenz	
Cpd I	FLG	Nevirapine	
Cpd I	FLG	(+)-Calanolide A or B	
Cpd I	FLG	Capravirine	
Cpd I	FLG	GW-695634	
Cpd I	FLG	MIV-150	
Cpd I	FLG	MV026048	
Cpd I	FLG	NV-05	
Cpd I	FLG	R-278474	
Cpd I	FLG	RS-1588	
Cpd I	FLG	TMC-120/125	
Cpd I	FLG	TMC-125	

Cpd I	FLG	UC-781	
Cpd I	FLG	YM-215389	
Cpd I	FLT	PA-457	Ritonavir
Cpd I	FLT	KPC-2	Ritonavir
Cpd I	FLT	HGTV-43	Ritonavir
Cpd I	FLT	Delavirdine	Ritonavir
Cpd I	FLT	Efavirenz	Ritonavir
Cpd I	FLT	Nevirapine	Ritonavir
Cpd I	FLT	(+)-Calanolide A or B	Ritonavir
Cpd I	FLT	Capravirine	Ritonavir
Cpd I	FLT	GW-695634	Ritonavir
Cpd I	FLT	MIV-150	Ritonavir
Cpd I	FLT	MV026048	Ritonavir
Cpd I	FLT	NV-05	Ritonavir
Cpd I	FLT	R-278474	Ritonavir
Cpd I	FLT	RS-1588	Ritonavir
Cpd I	FLT	TMC-120/125	Ritonavir
Cpd I	FLT	TMC-125	Ritonavir
Cpd I	FLT	UC-781	Ritonavir
Cpd I	FLT	YM-215389	Ritonavir
Cpd I	FLG	PA-457	Ritonavir
Cpd I	FLG	KPC-2	Ritonavir
Cpd I	FLG	HGTV-43	Ritonavir
Cpd I	FLG	Delavirdine	Ritonavir

Cpd I	FLG	Efavirenz	Ritonavir
Cpd I	FLG	Nevirapine	Ritonavir
Cpd I	FLG	(+)-Calanolide A or B	Ritonavir
Cpd I	FLG	Capravirine	Ritonavir
Cpd I	FLG	GW-695634	Ritonavir
Cpd I	FLG	MIV-150	Ritonavir
Cpd I	FLG	MV026048	Ritonavir
Cpd I	FLG	NV-05	Ritonavir
Cpd I	FLG	R-278474	Ritonavir
Cpd I	FLG	RS-1588	Ritonavir
Cpd I	FLG	TMC-120/125	Ritonavir
Cpd I	FLG	TMC-125	Ritonavir
Cpd I	FLG	UC-781	Ritonavir
Cpd I	FLG	YM-215389	Ritonavir

In the above given Tables 1 to 6 the term "FLG" is 2',3'-dideoxy-3'-fluoroguanosine, or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.